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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Paszty *et al.*

Serial No.: 09/818,954 Group Art Unit No.: 1647

Filed: March 27, 2001 Examiner: L. Spector, Ph.D.

For: NUCLEIC ACID MOLECULES ENCODING BETA-LIKE GLYCOPROTEIN HORMONE POLYPEPTIDES AND HETERODIMERS THEREOF

Docket No.: A-676B

DECLARATION UNDER 37 CFR §1.132 OF CHRIS PASZTY, Ph.D.

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Chris Paszty, hereby declare as follows:

1. I am currently employed as a research scientist at Amgen Inc. in Thousand Oaks, California, where I have worked since 1998. I earned a Bachelor of Science degree in Biology from University of Toronto in 1983, a Master degree in Genetics & Cell Biology from Washington State University in 1989, and a Ph.D. in Genetics & Cell Biology from Washington State University in 1991. After receiving my Ph.D., I did postdoctoral research with Dr. Edward Rubin and Dr. Mohandas Narla in the Human Genome Center at Lawrence Berkeley National Laboratories from 1992 to 1998. A copy of my *Curriculum Vitae* is attached hereto as Exhibit 1.

EXPRESS MAIL CERTIFICATE

"Express Mail" mail labeling number: EL 732696048 US Date of Deposit: September 17, 2004

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Joyce Murphy-Vogel
Printed Name

Signature

2. I am a co-inventor on U.S. Patent Application Serial No. 09/818,954, and have reviewed the patent application, including the pending claims.

3. It is my understanding from Amgen's attorneys and from reviewing Patent Office correspondence that the Patent Office has rejected claims 1-8, 11, and 48-50 in the patent application. I have read the Patent Office correspondence, and understand that it states the invention in the patent application is obvious based either on Mahairas *et al.* (locus AQ495547) alone, or in combination with an international patent application filed in the name of Sibson *et al.* (WO94/01548).

4. I have read both the Mahairas and Sibson references, and am familiar with their content. I make this Declaration to respond to the Patent Office's comments alleging that the present invention is obvious in view of what is taught by Mahairas and Sibson. By virtue of my education, training, and experience, I believe that I am competent to offer opinions about what average practitioners in my field (who would at least have a doctorate degree and significant research experience) would think about the expressed opinions in the Office Action.

5. In my opinion, one skilled in the art would not view the present invention obvious based upon the content of Mahairas. Mahairas describes a BAC clone that contains a fragment of human genomic DNA. The DNA sequence in Mahairas is not annotated, and doesn't identify any reading frames, or cloning orientation, nor homologies to other molecules. Also, I noticed that Mahairas' genomic DNA was not obtained by cDNA cloning. I also noticed that a number of cysteine residues important for activity (at positions 12, 36, and 40 of Sequence Id No: 3; described in Figure 3) are not present in the Mahairas molecule. In my opinion, Mahairas describes a piece of genomic DNA which if translated would result in an inactive, incomplete, non-mature form of the β10 polypeptide, which would not be able to adopt the necessary cystine-knot configuration. The 3-dimensional structure of the protein encoded by the fragment found in the Mahairas genomic DNA fragment is in my opinion completely unlike that of the mature β10 polypeptide described in the patent application, and would be inactive with regards to heterodimerizing with α2 polypeptide, binding to the α2/β10 receptor(s),

and the regulation of thyroidal function or promotion of thyroid differentiation or proliferation.

6. I understand that the Office Action interprets the Sibson patent application as teaching the use of a desired cDNA sequence in an expression vector, transfection into a host cell, and subsequent expression of the encoded protein. The Office Action says that Sibson covers "DNAs such as that disclosed by Mahairas, which are obtained by cDNA cloning".

7. In my opinion, it would not have been obvious to one skilled in the art to arrive at the invention in Amgen's patent application either from the Mahairas reference alone, or in combination with the Sibson document. I find no reason to believe that a person skilled in the art would even be motivated to combine the teachings of these two documents. I find no suggestion in either Mahairas or Sibson to do so, and I also find lacking any expectation that such a combination would be successful.

8. In forming this conclusion, I note that the Mahairas document describes a fragment of genomic DNA, which contains an intron, has no open reading frame specified, no annotations, and no orientation. No function or activity is provided by Mahairas. This DNA corresponds to a genomic fragment of the β10 gene, which upon expression would not be properly folded. Sibson relates to entirely unrelated cDNA (not genomic DNA) sequences. In my opinion, there is absolutely no suggestion in the documents cited by the Patent office to combine Sibson's teaching with genomic DNA fragments, let alone a β10 genomic DNA fragment.

9. I therefore conclude that there is no suggestion in the cited references to combine the teachings of Mahairas and Sibson. Even if someone skilled in the art did combine these references, the resulting combination of Mahairas and Sibson would in my opinion result in a misfolded, inactive peptide fragment, nothing even remotely resembling the invention in the Amgen patent application.

10. I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statement and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Christopher J. R. Paszty, Ph.D.

9/17/2004

Date

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EXHIBIT 1

CURRICULUM VITAE OF CHRIS PÁSZTY, PH.D.

Dept. of Metabolic Disorders
Amgen Inc.
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cpaszty@amgen.com

Education

- Ph.D. (Genetics & Cell Biology) 1991 Washington State University
- M.S. (Genetics & Cell Biology) 1989 Washington State University
- B.Sc. (Biology) 1983 University of Toronto, Canada

Awards & Honors

- Amgen Stock Option Special Recognition Award. 2004
- Amgen Stock Option Special Recognition Award. 2003
- Amgen VEP Special Recognition Award. 2003
- ENDO Meeting Oral Presentation Abstract selected (top 5%) for inclusion in Media Book. 2002
- Amgen Stock Option Special Recognition Award (top 10% of employees). 2002
- Amgen VEP Special Recognition Award (top 15% of employees). 2002
- Amgen Stock Option Special Recognition Award. 2001
- Amgen Spot Stock Recognition Award. 2000
- Amgen Stock Option Special Recognition Award. 2000
- Amgen VEP Special Achievement Award. 1999
- Amgen Spot Stock Recognition Award. 1999
- First & Corresponding author *Science* paper reviewed in "Research News" section, *Science*. 1997
- Significant national and international media coverage of results reported in *Science* paper. 1997
- Invited review articles. 1997 (see Publications section)
- Numerous Invited / Plenary Talks, (see Oral Presentations section)

Patent Applications

Bone and cartilage disease utility for secreted protein.
(Amgen Inc. patent application, 2002)

Novel member of the glycoprotein hormone receptor family.
(Amgen Inc. patent applications, 2000 & 2001)

Cloaked-2: novel cystine-knot protein.
(Amgen Inc. patent application, 2000)

Novel β-like member of the glycoprotein hormone family and heterodimer thereof.
(Amgen Inc. patent applications, 2000 & 2001)

Novel α-like member of the glycoprotein hormone family.
(Amgen Inc. patent application, 1999)

Professional Experience

Research Scientist IV 2002-present
Amgen Inc., Thousand Oaks, CA

Research Scientist III 2000-2002
Amgen Inc., Thousand Oaks, CA

Research Scientist I 1998-2000
Amgen Inc., Thousand Oaks, CA

Scientist 1997-1998
Human Genome Center, Lawrence Berkeley Laboratory, University of California, Berkeley, CA

Postdoctoral Fellow 1992-1997
Human Genome Center, Lawrence Berkeley Laboratory, University of California, Berkeley, CA

Graduate Student 1984-1991
Genetics and Cell Biology, Washington State University, WA

Oral Presentations

Plenary Sessions and other Invited Talks

Novel genes; Bone biology
ASBMR Meeting on Advances in Skeletal Anabolic Agents (2004, Bethesda, MD)
American Society for Bone and Mineral Research, Annual Meeting (2003, Minneapolis, MN)
The Endocrine Society's Annual Meeting (2002, San Francisco, CA)

Engineering the mouse genome. Models of human disease. Improved therapies.
Red Cell Gordon Research Conference (1997, Tilton, NH)
25th Anniversary Meeting of the National Sickle Cell Program (1997, Washington, DC)
American Society of Hematology (1996, Orlando, FL)
Plenary Session. American Society of Human Genetics (1996, San Francisco, CA)
Plenary Session. National Sickle Cell Disease Conference (1996, Mobile, AL)
Symposium: Future of Thalassemia Treatment (1995, Childrens Hospital, Oakland, CA)
Symposium: α-Thalassemia. International Society of Hematology (1995, Istanbul, Turkey)
Red Cell Gordon Research Conference (1995, Plymouth, NH)
American Society of Hematology (1994, Nashville, TN)

Publications

Auffray, I., Marfatia, S., de Jong, K., Lee, G., Huang, C-H., **Pászty, C.**, Tanner, M.J.A., Mohandas, N., and J. A. Chasis. 2000. *Glycophorin A dimerization and band 3 interaction during erythroid membrane biogenesis: in vivo studies in human glycophorin A transgenic mice.* Blood 97: 2872-2878.

Zhu, Y., **Pászty, C.**, Turetsky, T., Tsai, S., Kuypers, F., Lee, G., Cooper, P., Gallagher, P., Stevens, M., Rubin, E., Mohandas, N. and W. Mentzer. 1999. *Stomatocytosis is absent in "Stomatin"-deficient murine red blood cells.* Blood 93: 2404-2410.

Shi, Z., Afzal, V., Coller, B., Patel, D., Chasis, J., Parra, M., Lee, G., **Pászty, C.**, Stevens, M., Walensky, L., Peters, L., Mohandas, N., Rubin, E. M. and J. Conboy. 1999. *Protein 4.1R-deficient mice are viable but have erythroid membrane skeleton abnormalities.* J. Clin. Invest. 103: 331-340.

Embury, S., Mohandas, N., **Pászty, C.**, Cooper, P. and A. Cheung. 1999. *In vivo blood flow abnormalities in the transgenic knockout sickle cell mouse.* J. Clin. Invest. 103: 915-920.

Whitney, J. B., Leder, A., Lewis, J., Popp, R. A., **Pászty, C.**, Rubin, E. M., Shehee, W. R., Townes, T. M. and O. Smithies. 1998. *Rapid genotyping of mice with hemoglobinopathies and globin transgenes.* Biochemical Genetics. 36: 65-77.

Pászty, C., Brion, C. M., Witkowska, E., Manci, E., Stevens, M. E., Mohandas, N. and E. M. Rubin. 1997. *Transgenic knockout mice with exclusively human sickle hemoglobin and sickle cell disease.* Science. 278: 876-878.

Pászty, C. 1997. *Transgenic and gene knock-out mouse models of sickle cell anemia and the thalassemias.* Current Opinion in Hematology. 4: 88-93.

Pászty, C. 1997. *Mouse models for the α- and β-thalassemias: the power of transgenic and gene knock-out approaches.* Int. J. Pediatric Hematology/Oncology. 4: 75-84.

Fabry, M. E., Kennan, R. P., **Pászty, C.**, Costantini, F., Rubin, E. M., Gore, J. C. and R. L. Nagel. 1996. *Magnetic resonance evidence of hypoxia in a homozygous α-knockout of a transgenic mouse model for sickle cell disease.* J. Clin. Invest. 98: 2450-2455.

Mohandas, N. and **C. Pászty.** 1996. *Sickle cell disease: a step closer to the dream.* J. Clin. Invest. 97: 1135.

Morrison, J., **Pászty, C.**, Stevens, M. E., Hughes, S. D., Forte, T., Scott, J. and E. M. Rubin. 1996. *Apolipoprotein B RNA editing enzyme-deficient mice are viable despite alterations in lipoprotein metabolism.* Proc. Natl. Acad. Sci. 93: 7154-7159.

Loring, J. F., **Pászty, C.**, Rose, A., McIntosh, T. K., Murai, H., Pierce, J. E. S., Schramm, S. R., Wymore, K., Lee, V. M. Y., Trojanowski, J. Q. and K. R. Peterson. 1996. *Rational design of an animal model for Alzheimer's disease: introduction of multiple human genomic transgenes to*

reproduce AD pathology in a rodent. Neurobiology of Aging 17: 173-182.

Pászty, C., Mohandas, N., Stevens, M. E., Loring, J. F., Liebhaber, S. A., Brion, C. M. and E. M. Rubin. 1995. *Lethal α-thalassaemia created by gene targeting in mice and its genetic rescue.* Nature Genetics 11: 33-39

Pászty, C., Maeda, N., Verstuyft, J. and E. M. Rubin. 1994. *Apolipoprotein AI transgene corrects apolipoprotein E deficiency-induced atherosclerosis in mice.* J. Clin. Invest. 94: 899-903.

Daniell, H., Kaliappan, S. B., Krishnan, M. and **C. Pászty**. 1993. *A novel method to study DNA replication in vivo in organelles.* Nucleic Acids Res. 21: 1503-1504.

Pászty, C. and P. F. Lurquin. 1990. *Inhibition of transgene expression in plant protoplasts by the presence in cis of an opposing 3' promoter.* Plant Science 72: 69-79.

Lurquin, P. F. and **C. Pászty**. 1988. *Electroporation of tobacco protoplasts with homologous and nonhomologous transformation vectors.* J. Plant Physiol. 133: 332-335.

Xu, B., **Pászty C.** and P. F. Lurquin. 1988. *A plasmid-based method to quantitate homologous recombination frequencies in gram-negative bacteria.* BioTechniques 6: 752-760.

Pászty, C. and P. F. Lurquin. 1987. *Improved plant protoplast plating/selection technique for quantitation of transformation frequencies.* BioTechniques 5: 716-718.